Remarks

Claims 1-8, 11 and 42-45 are under consideration.

Claim 1 is amended to further define the invention and to provide an antecedent for dependent claim 8.

Claim 2 is cancelled as redundant in view of the amendments to claim 1.

Claim 7 is amended to obviate an inadvertent typographical error. Full support for the amendment is found in original claim 7.

The indication that claim 42 defines allowable subject matter is noted with appreciation. To expedite allowance, claim 42 is rewritten in independent form.

Claims 43-45 are new. These three claims are dependent on allowable claim 42, are modeled after original claims 5, 6 and 7, and should be allowable as well.

It is hereby requested that the Notice to Comply that accompanied the aforesaid Office Action be withdrawn because SEQ ID Nos are presented in FIGURES 8, 9 and 10. This fact was confirmed during a telephone conference with Examiner Dibrino on May 9, 2011.

The rejection of claim 8 under 35 U.S.C. 112, Second Paragraph, is deemed to have been overcome by the present amendment to claim 1 which now provides sufficient antecedent basis for the language of claim 8.

The rejection of claims 1 and 3-7 under 35 U.S.C. 102(b) as anticipated by Rhode *et al.* is not warranted, and is hereby traversed.

Anticipation requires that each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *In re Robertson*, 169 F.3d 743, 745, 49 U.S. P.Q. 2d 1949 (Fed. Cir. 1990). Thus, unless all the elements of the rejected claim are disclosed by the cited reference, a basis for an anticipation rejection does not exist. That is the case here.

As can be seen from FIGURE 1 in Rhode *et al.*, this publication describes fusion polypeptides that include an antigenic peptide as well as Class II α and β subunits. Described is an attempt to integrate into a single construct the MHC binding domains and the antigenic peptide. The constructs discussed in Rhode *et al.* are able to form the binding

domains of the MHC molecule. In contradistinction, the present claims as amended define isolated fusion proteins that are free from the binding domains of the MHC molecule.

The further rejection of claims 1, 7 and 11 under 35 U.S.C. 102(b) as anticipated by WO 94/25054 A1 by Atkin, likewise is not warranted, and is traversed.

Here again, the recombinant vaccines described by Atkin are fusion proteins that include the binding domains of the MHC molecule whereas the present claims do not.

As noted in the specification, the binding domain of the MHC II molecule is defined as having been formed by the α1 and β1 domains of the MHC II molecule (See, for example, page 18, lines 24-26). Inasmuch as α2 and β2 are also important for stabilizing the structure of the binding domain, the MHC II binding domain also includes these particular subdomains (See page 18, lines 26-31). Thus, the MHC II binding domain essentially includes the extracellular domain of the MHC II molecule (page 18, lines 31-34). Likewise, the MHC I binding domain is described in the specification at page 18, lines 31-34.

WO 94/25054 by Atkin describes three different constructs said to be useful for inducing an immune response against an antigenic peptide, designated as "target sequence." This antigenic peptide is either covalently linked to an MHC molecule or is associated, directly or indirectly, with the MHC molecule (Atkin, page 6, lines 6-13). Such constructs, containing an antigenic peptide covalently linked to an MHC molecule contain sequences that are responsible for mediating the binding of MHC I to CD8, or sequences responsible for mediating the binding of MHC II to CD4. See, for example, Atkin at page 7, lines 5-10 and page 7, line 24 to page 8, line 5. The Atkin constructs contain as an essential element an amino acid sequence which provides interaction with the T-cell receptor (T-lymphocyte MHC product receptor). Atkins expressly states that "said amino acid sequence providing interaction with MHC product receptor may be either CD8 binding sequence derived from the amino acid sequence of the MHC Class I product or CD4 binding sequence derived from amino acid sequence of the MHC Class II product. *Id.*

Without exception, these amino acid sequences responsible for binding MHC I to CD8 and MHC II to CD4 are located in the extracellular domain of the MHC Molecule which domain is not present in the presently claimed fusion protein. Accordingly, there can be no anticipation of the present claims by WO 94/25054 by Atkin.

WO 94/25054 by Atkin also is speculative and lacks enablement. Examples demonstrating the capability of the therein described fusion proteins to induce an immune response against an antigenic peptide (the "target sequence") are lacking. In contradistinction, examples in the present application amply demonstrate that the claimed fusion proteins, containing an antigen and a portion of the MHC molecule that lacks the entire extracellular domain of the MHC molecule, are extremely effective in stimulating production of $CD4^+$ and $CD8^-$ lymphocytes.

The rejection of claims 1, 3-7 and 11 under 35 U.S.C. 103(a) as unpatentable over Rhode *et al.* in view of US 2002/0110566 A1 is traversed as well.

Obviousness is a question of law based on underlying factual inquires. In putting forth a *prima facie* case, the Examiner serves as a factfinder and makes what are usually referred to as the three *Graham* factual inquiries. *Graham v. John Deere,* 383 U.S. 1.17, 148 U.S.P.Q. 459 (1966). See also M.P.E.P. §2141. The required fact findings are clearly lacking in this case.

The first step in *Graham* obviousness analysis is to determine the scope and content of the prior art. The prior art includes patents and printed publications having effective dates prior to the date of invention of the patent at issue. The scope of the prior art includes references that are "from the same field of endeavor, regardless of the problem addressed, [or] reasonably pertinent to the particular problem with which the inventor is involved." *In re Clay,* 966 F.2d 656, 659, 23 USPQ2d 1058, 1060 (Fed. Cir. 1992).

The second step of *Graham* obviousness analysis is to determine the differences between the prior art and the claimed invention. This is performed by comparing the claimed invention to the prior art.

The third step is to determine the level of ordinary skill in the relevant art. The level of ordinary skill is determined from several factors, including the sophistication of the technology involved and the educational background of those active in the field. *Orthopedic Equipment Co. v. United States,* 702 F.2d 1005, 1011, 217 USPQ 193 (Fed. Cir. 1983); *Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.,* 807 F.2d 955, 962, 1 USPQ2d 1196, 1201 (Fed. Cir. 1986); *see also In re GPAC Inc.,* 57 F.3d 1573, 1579, 35 USPQ2d 1116,

1121 (Fed. Cir. 1995). The level of ordinary skill is used to determine whether, given the prior art, the invention as a whole would have been obvious at the time that it was made.

After the above three fact inquiries have been made, a legal determination of obviousness is made. According to the Federal Circuit, "[w]hat matters in the § 103 obviousness determination is whether a person of ordinary skill in the art, having all the teachings of the [prior art] references before him, is above to produce the structure defined by the claim." *Orthopedic*, 702 F.2d at 1013, 217 USPQ at 200. While a rigid approach relating to a finding of a teaching, suggestion or motivation has been rejected, the Supreme Court recently stated that "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

A rationale that supports the conclusion of obviousness is lacking in this case. An articulation of a rationale is especially important when references or teachings are combined to render an invention obvious. An example of a rationale supporting obviousness based on a combination of references is when the references themselves teach, suggest or would motivate one to make such a combination. The Supreme Court has made clear that this so-called TSM test is not exclusive, and that other rationales may be used to support a conclusion of obviousness. *See KSR*, 550 U.S. at 418. In this case, however, no valid rationale supporting a conclusion of obviousness has been advanced by the Examiner.

In order to establish a *prima facie* case for obviousness, all claim limitations must be taught or suggested by the prior art. *In re Royka*, 180 U.S.P.Q. 580 (C.C.P.A. 1974). The Examiner's burden of proof is manifold. The Examiner must demonstrate that the cited prior art includes "a suggestion of all the elements in a claim." *CFMT Inv. v. Yieldup Int'l Corp.*, 68 U.S.P.Q.2d 1333, 1342 (Fed. Cir. 2003). The Examiner must also provide evidence that would demonstrate "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in a way the claimed new invention does." *KSR*, 550 U.S. at 418, 82 U.S.P.Q. 2d at 1396. "To facilitate review, this analysis should be made explicit." *Id.* "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulate reasoning with some rational underpinning

to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988, 78 U.S.P.Q.2d 1329, 1336 (Fed. Cir. 2006). Here, the Examiner has failed to do that.

The following requirements must be satisfied to establish a *prima facie* case of obviousness. First, "a court must ask whether the improvement is more than predictable use of prior art elements according to their established functions. ... [I]t [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *KSR*, 550 U.S. at 418-19, 82 U.S.P.Q.2d at 1396. Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 U.S.P.Q. 2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). These requirements are not satisfied in this case. In particular, as pointed out hereinabove, Rhode, *et al.* does not teach an isolated fusion protein that is free from a binding domain of the MHC molecule.

As acknowledged by the Examiner, Rhode, *et al.* does not teach that the protein described therein is in a composition that contains a pharmaceutically acceptable carrier. Accordingly, Rhode, *et al.* provides no valid basis whatsoever for the attempted combination of the teachings of Rhode, *et al.* with those of US 2002/0110566 by Neele, *et al.*

In any event, Neele, *et al.* fails to cure the deficiencies of Rhode, *et al.* as a reference against claims 1, 3-7 and 11 for the reasons advanced hereinabove as well as those discussed hereinbelow.

Rhode, *et al.* mentions throughout the applied publication that the correct conformation of their fusion molecule was confirmed (df. E.g., Abstract of Rhode, et al.:

"Correct conformation of these molecules was verified" and page 4889, 2nd Column, end of 3rd paragraph: "linking these polypeptide chains does not interfere with their ability to fold properly"). This is in keeping with the established teaching in the art that antigenic peptides must be presented to T cells in the context of a correctly folded extracellular domain of an MHC molecule. Rhode, *et al.* did not remove the extracellular binding domain of their MHC fusion protein but, instead, preserved the binding domain and its conformation. Therefore based on the teachings of Rhode, *et al.*, the extracellular scaffold into which the antigenic peptide is integrated would have been considered an essential element that the skilled artisan would not have modified because the fusion protein's capability of mediating a T cell response might be lost.

In view of this generally accepted principle regarding the extracellular binding domain, the results disclosed in the present application are indeed surprising. Using a fusion protein as specified in amended claim 1, i.e., a protein containing an antigenic peptide fused to a transmembrane domain and a cytoplasmic domain of an MHC molecule but lacking the entire binding domain of an MHC molecule, the inventors of the present application demonstrate a very significant stimulation and proliferation of $CD4^+$ and $CD8^+$ T-lymphocytes (cf. Examples 1 to 4). Considering the teachings of Rhode, *et al.* such a T cell response is quite unexpected, in particular because a strong T cell response could be observed, even in the absence of a correctly folded binding pocket.

At the time this invention was made, cell surface expression of a fusion protein containing a single MHC II α-chain TM domain was known to require co-expression of an MHC II β-chain TM domain. In this regard, Rhode, *et al.* points out that their fusion proteins containing a single MHC II α-chain TM domain could only be rescued from intracellular compartments, probably because they contained in the extracellular portion a flexible linker connecting the β- and α-chains of an MHC molecule (cf. Page 4890, 1st Column, 2nd Paragraph of Rhode, *et al.*). The results demonstrated in the present application, i.e., that fusion proteins according to the definition of amended claim 1 are indeed capable of inducing a very strong stimulation and proliferation of $CD4^+$ and $CD8^+$ T-lymphocytes, would have been unexpected to the skilled artisan since stimulation of T-lymphocytes was known to require cell surface expression.

Withdrawal of the rejection based on 35 U.S.C. 103(a) is requested.

No additional claim fees are believed to be due in view of the prior cancellation of claims 12-18 and the fact that these are only two independent claims in this application. In the event an additional claim fee is required, kindly charge any such additional claim fee to our Deposit Account No. 15-0508.

The foregoing Amendment to the claims and the accompanying discussion are believed to dispose of all issues in this case and to place this application in condition for allowance. Early such action is solicited.

Respectfully submitted,

Dated: June 13, 2011

By _____
Talivaldis Cepuritis (Reg. No. 20,818)

OLSON & CEPURITIS, LTD.
20 North Wacker Drive
36th Floor
Chicago, Illinois 60606
(312) 580-1180

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this AMENDMENT UNDER RULE 111 is being transmitted by facsimile transmission to Fax No. 571-273-8300 on June 13, 2011.

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Talivaldis Cepuritis (Reg. No. 20,818)